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2. Patent application number *(The Patent Office will fill in this part)* — **9822458.7**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Imperial College Innovations Limited
Sherfield Building
Imperial College
London
SW7 2AZ
United Kingdom

Patents ADP number *(if you know it)* 7409436 002

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — METHODS OF TREATMENT

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
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NOTTINGHAM
NG1 5DD

Patents ADP number *(if you know it)* 1305010

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
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11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date

ERIC POTTER CLARKSON 15 October 1998

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METHODS OF TREATMENT

The renin-angiotensin system (RAS) is well known and is described in text books of physiology and medicine. In brief, renin acts on angiotensinogen to generate angiotensin I (ATI). This peptide is converted to angiotensin II by the action of angiotensin converting enzyme (ACE). ATII stimulates the release of aldosterone, and it is also a potent vasoconstrictor. ATII exerts at least some of its effects through the ATII receptors.

The RAS is involved in the maintenance and control of blood pressure as well as the regulation of salt and water balance.

The renin angiotensin system (RAS) and chronic heart failure (CHF)

Early in chronic heart failure activation of the RAS occurs, initially mainly due to the introduction of heart failure treatment with drugs, particularly diuretics. It is well known that ACE inhibitors exert survival benefit in CHF patients, and one major mode of action is thought to be via its inhibiting effect on the RAS.

Recently (1997), we have shown [1] that, when considering the conventional disease severity markers peak oxygen consumption, LVEF, and NYHA class, none of these markers very strongly related to plasma renin activity and aldosterone plasma levels. However, the presence of cardiac cachexia, i.e. significant non-intentional non-oedematous weight loss (>7.5% of the previous normal weight), related closely to the presence of very high plasma renin activity and aldosterone plasma levels. Non-cachectic patients with CHF did show intermediately raised levels of plasma renin activity and aldosterone. This difference is found despite cachectic and non-cachectic patients being very similarly treated with ACE inhibitors. "ACE escape" - i.e. "angiotensin II escape" or "aldosterone escape" may be the reason, i.e. the RAS may stay activated even if patients are treated with agents blocking the main pathway of the RAS (ACE inhibitors). This finding could be particularly relevant for the development of cachectic disorders. There are no published data available on this issue in any cachectic disorder.

Aldosterone and angiotensin II may "escape" during ACE inhibitor treatment (via ACE independent pathways) [2], i.e. in the short term their plasma levels are reduced (to a varying degree), but in the long-term plasma levels may increase again.

The main bioactive element of the RAS is angiotensin II (AT II). Elevations of AT II in plasma or in local tissue would indicate conditions in which inhibition of the RAS may have significant therapeutic benefit even where partial inhibition of the RAS has been achieved (such as by therapy

with angiotensin converting enzyme [ACE] inhibitors).

RAS / AT II and wasting and weight loss in CHF patients

AT II can directly and indirectly contribute to the development of body wasting. Firstly, AT II can directly induce apoptosis, i.e. programmed cell death. Secondly, elevated AT II could on the tissue level down-regulate local production of insulin-like growth factor-I (IGF-I). IGF-I is known to be a major factor protecting against apoptosis and it is itsellf strongly protein anabolic.

The detrimental effects of angiotensin II and aldosterone are similar, nevertheless these adverse effects may at least in part be independent of each other. For instance, aldosterone is known to independently reduce magnesium levels by increasing urinary magnesium output, hence magnesium depletion is a prominent feature of many CHF patients [3].

Results for Angiotensin II analysis

The activation status of the RAS as a potential cause of body wasting due to underlying disease has never been studied. We have studied a variety of cachectic conditions - for instance due to chronic heart failure, AIDS, liver cirrhosis, and cancer - and we have found activation of the RAS as evidenced by elevated plasma AT II levels (mean AT II plasma levels were clearly above the upper limit of the normal range, see Figure 1). This is not dependent on any specific aetiology for the cachectic disorder, in fact we find elevated AT II plasma levels (i.e. RAS activity) also in cases of idiopathic cachexia, i.e. cachexia of unknown origin. Nevertheless, we find the activation of the RAS to be specific for cachectic disorders, as it is not seen in patients with a similar degree of weight loss consequent upon malnutrition.

Method to measure AT II:

Blood samples were collected after supine rest of at least 10 minutes. An antecubital polyethylene catheter was inserted and 10 ml of venous blood were drawn. After immediate centrifugation aliquots (EDTA plasma sample) were stored at -70°C until analysis. Angiotensin II was measured using a commercially available radioimmunoassay (IBL, Hamburg, Germany, sensitivity 1.5

pg/ml). After extraction of the plasma samples, AT II is assayed by a competitive radioimmunoassay . This radioimmunoassay is using a rabbit anti-AT II antiserum and a radio-iodinated AT II tracer. Bound and free phases are separated by a second antibody bound to solid phase particles, followed by a centrifugation step. The radioactivity in the bound fractions is measured and a typical standard curve can be generated. The test has a cross-reactivity with AT I of <0.1% and a within and between run reproducibility between 3.9 and 8.6%. The reference range for healthy subjects is 20 to 40 pg/ml.

Invention / claims

to use the following drugs or procedures in humans or mammals for
the treatment or prevention of weight loss due to underlying disease (cachexia) - these underlying diseases include for example, but not restricted to AIDS, liver cirrhosis, chronic obstructive pulmonary disease with or without emphysema, chronic renal failure, chronic infections (like pneumonia), cancer (i.e. cancer cachexia), and heart disease including hypertension and chronic heart failure (i.e. cardiac cachexia), and idiopathic cachexia (i.e. cachexia due to unknown disease).

1. ACE inhibitors
2. angiotensin II receptor antagonists

to use the following drugs or procedures in humans or mammals for
a) treatment or prevention of weight loss due to underlying disease (cachexia) - these underlying diseases include for example, but not restricted to AIDS, liver cirrhosis, chronic obstructive pulmonary disease with or without emphysema, chronic renal failure, chronic infections (like pneumonia), cancer (i.e. cancer cachexia), and heart disease including hypertension and chronic heart failure (i.e. cardiac cachexia), and idiopathic cachexia (i.e. cachexia due to unknown disease)
b) treatment or prevention of weight loss due to the ageing process
c) the enhancement of exercise performance in health

drugs or procedures that could reduce angiotensin II plasma levels and the activity of the RAS via mechanisms other than ACE inhibition and AT II receptor blockade

1. any drug with an inhibiting effect on aldosterone, e.g. aldosterone antagonists (like spironolactone)
2. chymase inhibitors
3. cathepsin B inhibitors
4. renin inhibitors
5. inhibitors of ACE alternative pathways
6. exercise training
7. electrical muscle stimulation

The drugs are administered to the patient in any suitable form or by any suitable route in order to have the desired effect. The invention also includes the use of the drug in the manufacture of a medicament for treating the patient as said.

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Drugs which inhibit the effect of aldosterone, chymase inhibitors, cathepsin B inhibitors, renin inhibitors, and inhibitors of ACE alternative pathways, are known in the art. Some are listed for example in the latest editions of the British National Formulary and in the latest edition of Martindale's Pharmacopeia

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Results for noradrenaline plasma level analysis

Chronic heart failure (CHF) is a complex disorder affecting an increasing number of patients in the community with a prevalence of 10 to 30% in people over the age of 65 years [1]. Multiple physiological pathways are pathologically affected, and a series of vicious cycles have been suggested that could transform cardiac abnormalities into haemodynamic, endocrine, immunological, and muscular abnormalities that all contribute to the clinical picture of chronic heart failure [2,3,4]. One of the most studied aspects is activation of the sympathetic nervous system (SNS). Activation of the SNS can be expressed in several different ways. Apart from measuring circulating catecholamines (particularly noradrenaline, adrenaline, and dopamine), it is possible to assess sympathetic nervous excitation directly by measuring nervel impulses [5], or indirectly by analysing heart rate and blood pressure variability [6]. The technique of assessing catecholamine levels has also been developed further by assessing the catecholamine spill-over using radio-labeled tracers [7]. Nevertheless, measurement of catecholamine levels at rest are the most widely used technique. In this respect it is important to note, that noradrenaline and adrenaline are not only released from the adrenal medulla (as hormones), but that they are also neurotransmitters that are released into the synaptic cleft of sympathetic post-ganglionic nerves (therefore also termed adrenergic). Only a small proportion of the synaptically released catecholamines spills over into the circulation. Therefore measured plasma concentrations of noradrenaline and adrenaline may in some circumstances grossly underestimate the local catecholamine concentration in the adrenergic synapses.

Catecholamines: from myocardial infarction to heart failure

Sympathetic activation is well recognised to be important contributing to the development of myocardial ischaemia [8]. Cardiac β-receptors mediate increases of heart rate and inotropy, that under normal conditions lead to coronary dilation to match the oxygen demand. The direct effect of catecholamines on the coronary blood vessel is vasoconstriction mediated via α-adrenoreceptors [9]. During exercise catecholaminergic vasoconstriction is mainly mediated through circulating catecholamines and not through local hormone release [10]. After the development of coronary plaques and stenosis, the vasodilatory flow reserve is reduced and the metabolic vasodilation is

more and more and more reduced as a result of α-adrenergic coronary vasoconstriction [11].

Considering the onset of an myocardial infarction as a condition of pain and mental and physical stress, it is not surprising that dramatic increases of catecholamine levels have been detected early after the onset of infarction in a variety of studies. Alone between 1969 and 1980, 15 studies with about 25000 patients and 5000 control subjects (see overview in [12]) have investigated plasma noradrenaline levels after myocardial infarction. Catecholamine levels peak within minutes to few hours after the onset of symptoms, and they continue to be raised for several days. The degree of the enzymatic changes during the myocardial infarction [13], i.e. severity of the heart attack, the early onset of ventricular arrhythmias [14], the development of cardiogenic shock [15], and of congestive heart failure [14,16] are all related to plasma catecholamine levels. In patients with myocardial infarction and clinical heart failure noradrenaline remains elevated for about 1 month [17]. Sedative treatment with morphines [18], and β-blockers [19] have long been known to be able to reduce catecholamine levels during acute myocardial infarction. Ischaemic heart disease is the most common cause of developing CHF.

When heart failure has fully developed it is then difficult to establish what exactly induces neurohormonal activation, as both the underlying disease process itself and the medication contribute to the complex hormonal alterations. Measurements in untreated patients have revealed that the sympathetic system is activated (raised catecholamine levels), but that in contrast the renin-angiotensin system is usually not activated [20,21]. The initial sensor to activate these alterations remains unclear, but it is known that in the absence of a neurohormonal body response the blood pressure would fall, i.e. tissue blood perfusion would be insufficient [22]. Therefore the initial triggers of neurohormonal activation in heart failure could be baroreceptors in the heart and aorta. When heart failure progresses other mechanisms may gain more importance. The baroreflex responses are blunted in stable chronic heart failure, whereas the peripheral and central chemoreflex sensitivity [23,24] as well as the metabo-ergoreceptor reflex (afferents sensitive to skeletal muscle work load) [25] deliver a strong sympathetic nervous input that may finally also lead to chronically raised catecholamine levels in sever chronic heart failure.

Catecholamines and weight loss in CHF patients

Only recently (1997), we have documented [26] that, when considering the conventional disease severity markers peak oxygen consumption, left ventricular ejection fraction (LVEF), and NYHA class, none of these markers very strongly related to resting noradrenaline and adrenaline levels. However, the presence of cardiac cachexia, i.e. significant non-intentional non-oedematous weight loss (>7.5% of the previous normal weight), related closely to the presence of raised catecholamine levels. Non-cachectic patients with CHF did on average not have elevated catecholamine levels.

Catecholamines can alter the metabolic status of the body, i.e. they can contribute to increased metabolic rates that may finally lead to a catabolic status and weight loss. This has never been considered to be a basic mechanism for body wasting in human disease in general.

Catecholamines and weight loss in wasting disorders

We have studied a variety of other cachectic conditions - for instance due to AIDS, liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, chronic infections (like pneumonia) and cancer - and we have found activation of the SNS as evidenced by elevated plasma noradrenaline levels (mean plasma levels were clearly above the upper limit of the normal range, see Figure). This is not dependent on any specific aetiology for the cachectic disorder, in fact we find elevated noradrenaline plasma levels (i.e. SNS activity) also in cases of idiopathic cachexia, i.e. cachexia of unknown origin. Nevertheless, we find the activation of the SNS to be specific for cachectic disorders, as it is not seen in patients with a similar degree of weight loss consequent upon malnutrition.

Method to measure noradrenaline:

Blood samples were collected after supine rest of at least 10 minutes. An antecubital polyethylene catheter was inserted and 10 ml of venous blood were drawn. After immediate centrifugation aliquots (EDTA plasma sample) were stored at -70°C until analysis. Noradrenaline was measured by reverse-phase high pressure liquid chromatography (HPLC) with electrochemical detection. The detectable limit was: 0.2 nmol/l. The within batch coefficient of variance of repeated measures is less than 5%, the between batch coefficient of variance for repeated measures is 9%. The upper

limit of normal for subjects (mean + 2 standard deviations of control group: 3.31 nmol/l).

Invention / claims

to use the following drugs or procedures in humans or mammals for

a) treatment or prevention of weight loss due to underlying disease (cachexia) - these underlying diseases include for example but not exclusively AIDS, liver cirrhosis, chronic obstructive pulmonary disease with or without emphysema, chronic renal failure, chronic infections (like pneumonia), cancer (i.e. cancer cachexia), and heart disease including hypertension and chronic heart failure (i.e. cardiac cachexia), and idiopathic cachexia (i.e. cachexia due to unknown disease)

b) treatment or prevention of weight loss due to the ageing process

c) the enhancement of exercise performance

d) prevention of weight loss consequent to cardiovascular disorders in patients at risk of heart disease including hypertension,

these drugs may be any compound that could reduce catecholamine plasma levels and the activity of the SNS

dyslipidaemia, and diabetes. Drugs in groups 1 to 5 and 7 to 10 are useful in this indication

1. Beta receptor blockers
2. imidazoline receptor antagonists (including moxonidine and rilmenidine)
3. centrally acting alpha receptor agonists like clonidine
4. peripherally acting alpha receptor antagonists
5. ganglion blocking agents
6. drugs that have effects on cardiovascular reflexes and thereby reduce SNS activity

- opiates (via chemoreceptor)
- digitalis alkaloids (via enhancement of baroreflex sensitivity)
- scopolamine
- anabolic growth factors like growth hormone and insulin-like growth factor-I (via effects on metabo-ergoreceptor)

7. ACE inhibitors
8. angiotensin receptor antagonists
9. aldosterone antagonists (like spironolactone)

10. tyrosine betahydroxylase

these procedures could be

1. exercise training

2. electrical muscle stimulation

The drugs are administered to the patient in any suitable form or by any suitable route in order to have the desired effect. The invention also includes the use of the drug in the manufacture of a medicament for treating the patient as said.

Drugs which are useful in the practice of the invention, such as those listed on pages 9 and 10 (classes 1 to 10), are well known and examples are included in the latest editions of the British National Formulary and in the latest edition of Martindale's (+)

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(+) Pharmacopia

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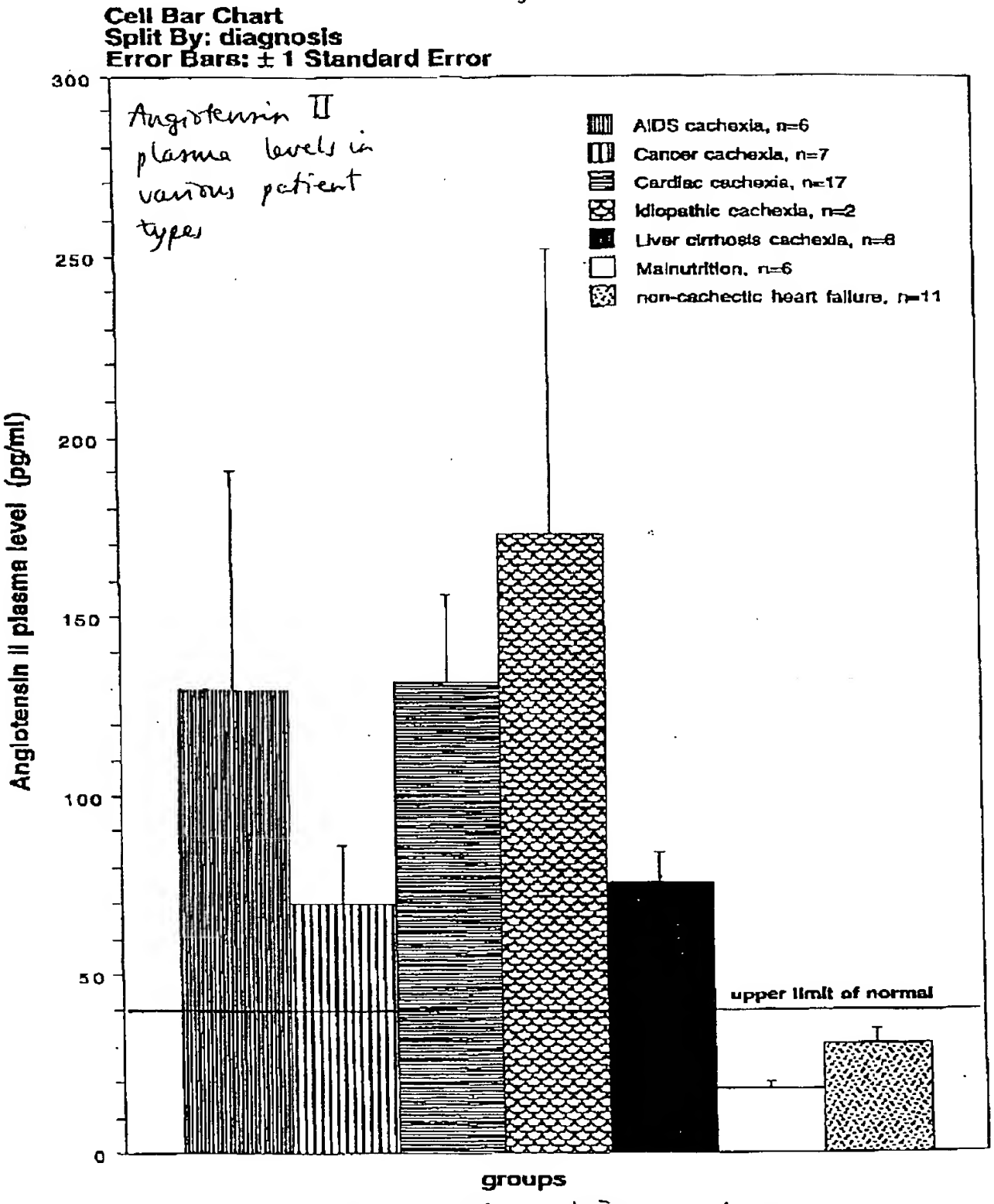
ACE inhibitors include alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fosinopril, lisinopril, moexipril, and the like. A particularly preferred ACE inhibitor is enalapril. Angiotensin receptor antagonists include candesartan, eprosartan, losartan, valsartan and the like. A particularly preferred angiotensin receptor anatagonist is losartan.

Figure 1



Patients with wasting disease have increased angiotensin II plasma levels

ANOVA Table for NA nnoM

	DF	Sum of Squares	Mean Square	F-Value	P-Value
[illegible] diag.- NA-figure	11	260.240	23.658	2.650	.0020
[illegible]idual	103	825.956	8.019		

Model II estimate of between component variance: 1.796
94 cases were omitted due to missing values.

Means Table for NA nnoM
Effect: Cachexia diag.- NA-figure

	Count	Mean	Std. Dev.	Std. Err.
AIDS	6	5.217	4.801	1.960
cachectic CHF	16	4.670	3.518	.880
Cancer	2	8.368	5.058	3.575
chronic renal failure	2	3.686	4.658	3.315
COPD	14	2.843	2.305	.616
healthy controls	16	1.940	.687	.172
Ideopathic cachexia	2	3.835	3.203	2.265
Infection	6	6.497	6.856	2.844
Liverclrh + Cachexia	6	6.098	5.603	2.324
Malnutrition	6	2.987	1.764	.726
more Controls	2	2.373	1.099	.884
nc CHF	37	2.694	1.944	.221

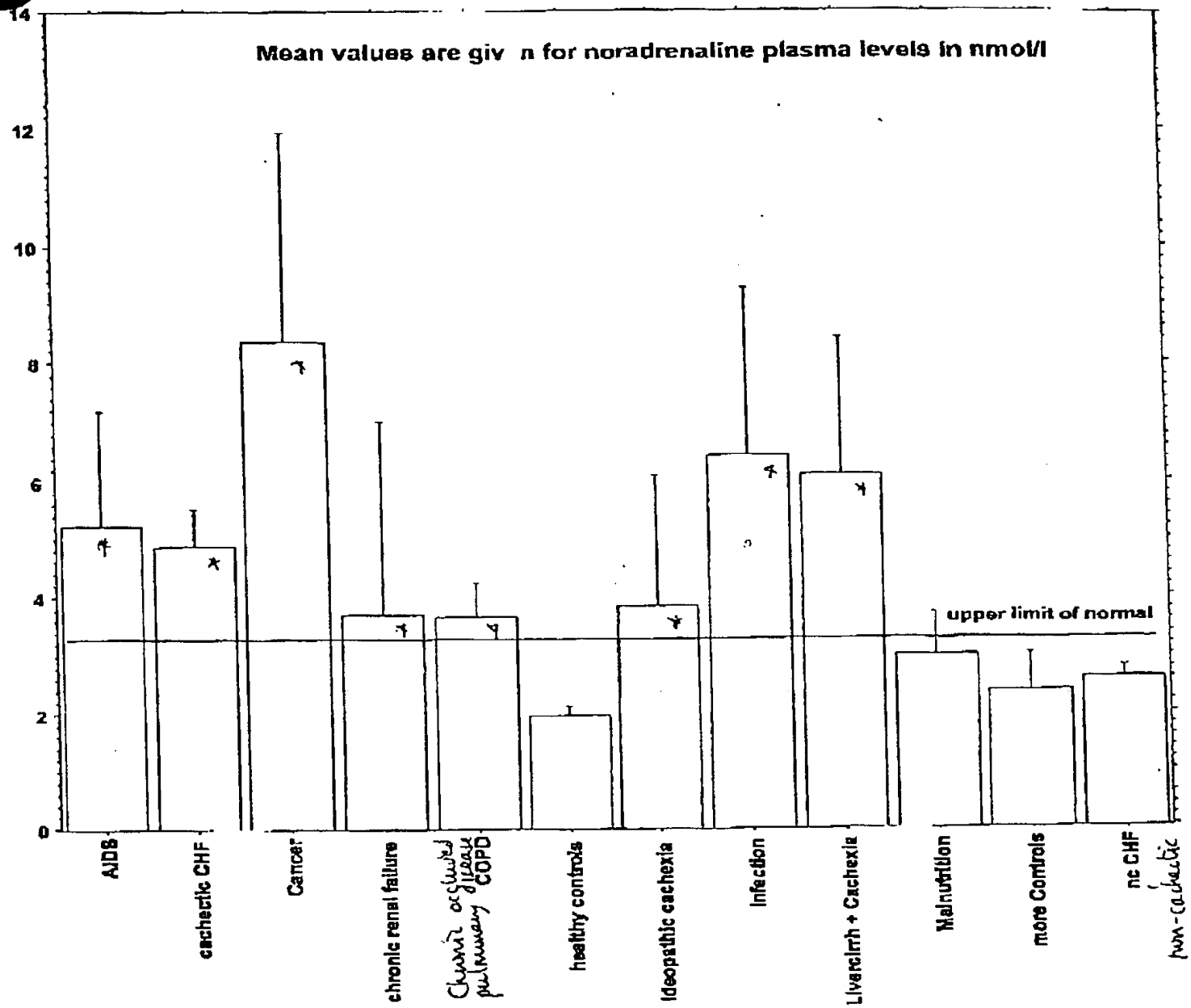
Figure 2

Individual data as summarized in Figure 3

Fisher's PLSD for NA nnoM
Effect: Cachexia diag.- NA-figure
Significance Level: 5 %

	Mean Diff.	Crit. Diff	P-Value	
AIDS, cachectic CHF	.547	2.718	.6004	
AIDS, Cancer	-3.148	4.588	.1783	
AIDS, chronic renal failure	1.532	4.588	.5119	
AIDS, COPD	1.374	2.748	.2575	
AIDS, healthy controls	3.277	2.688	.0174	S
AIDS, Ideopathic cachexia	1.382	4.588	.5514	
AIDS, Infection	-1.280	2.243	.4679	
AIDS, Liverclrh + Cachexia	-.882	2.243	.6909	
AIDS, Malnutrition	2.230	2.243	.1756	
AIDS, more Controls	2.843	3.071	.1668	
AIDS, nc CHF	2.523	2.472	.0371	S
cachectic CHF, Cancer	-3.698	4.928	.1042	
cachectic CHF, chronic renal failure	1.175	4.226	.8827	
cachectic CHF, COPD	1.227	2.087	.2462	
cachectic CHF, healthy controls	2.930	2.018	.0049	S
cachectic CHF, Ideopathic cachexia	1.035	4.228	.6283	
cachectic CHF, Infection	-1.687	2.713	.2547	
cachectic CHF, Liverclrh + Cachexia	-1.228	2.713	.3713	
cachectic CHF, Malnutrition	1.883	2.713	.1716	
cachectic CHF, more Controls	2.497	3.552	.1663	
cachectic CHF, nc CHF	2.286	1.719	.0099	S
Cancer, chronic renal failure	4.870	5.816	.1022	
Cancer, COPD	4.722	4.248	.0298	S
Cancer, healthy controls	5.425	4.912	.0031	S
Cancer, Infection	1.923	4.586	.4062	
Cancer, Liverclrh + Cachexia	2.267	4.586	.3292	
Cancer, Malnutrition	5.378	4.586	.0250	S
Cancer, more Controls	5.992	5.127	.0224	S
Cancer, nc CHF	5.781	4.077	.0058	S
chronic renal failure, COPD	.052	4.248	.9806	
chronic renal failure, healthy controls	1.755	4.212	.4105	
chronic renal failure, Ideopathic cachexia	-.140	5.816	.9607	
chronic renal failure, Infection	-2.742	4.586	.2384	
chronic renal failure, Liverclrh + Cachexia	-2.403	4.586	.3010	
chronic renal failure, Malnutrition	.708	4.586	.7600	
chronic renal failure, more Controls	1.922	5.127	.6103	
chronic renal failure, nc CHF	1.111	4.077	.5900	
COPD, healthy controls	1.703	2.056	.1085	
COPD, Ideopathic cachexia	-.192	4.248	.9285	
COPD, Infection	-2.794	2.740	.0458	S
COPD, Liverclrh + Cachexia	-2.455	2.740	.0766	
COPD, Malnutrition	.656	2.740	.8380	
COPD, more Controls	1.869	3.573	.4827	
COPD, nc CHF	1.058	1.782	.2362	
healthy controls, Ideopathic cachexia	-1.896	4.212	.3743	
healthy controls, Infection	-4.497	2.669	.0013	S
healthy controls, Liverclrh + Cachexia	-4.158	2.669	.0026	S
healthy controls, Malnutrition	-1.047	2.669	.4418	
healthy controls, more Controls	-.433	3.533	.6085	
healthy controls, nc CHF	-.644	1.680	.4491	
Ideopathic cachexia, Infection	-2.602	4.680	.2681	
Ideopathic cachexia, Liverclrh + Cachexia	-2.263	4.586	.3298	
Ideopathic cachexia, Malnutrition	.848	4.586	.7144	
Ideopathic cachexia, more Controls	1.462	5.127	.5730	
Ideopathic cachexia, nc CHF	1.251	4.077	.5441	
Infection, Liverclrh + Cachexia	.338	2.243	.8266	
Infection, Malnutrition	3.450	2.243	.0873	
Infection, more Controls	4.063	3.971	.0450	
Infection, nc CHF	3.853	2.472	.0026	
Liverclrh + Cachexia, Malnutrition	3.112	2.243	.0698	
Liverclrh + Cachexia, more Controls	3.725	3.971	.0857	
Liverclrh + Cachexia, nc CHF	3.515	2.472	.0058	
Malnutrition, more Controls	.613	3.971	.7600	
Malnutrition, nc CHF	.403	2.472	.7472	
more Controls, nc CHF	-.210	3.371	.9017	

Figure 3.



Chronic wasting disorders show increased activity of SNS as evidenced by increased plasma noradrenaline levels

* All of these cachectic disorders have ~~lower~~ mean plasma noradrenaline levels which are higher than normal

PCT/GB99/03302

22/10/99

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